

REMARKS

The Office Action of November 2, 2006 has been received and reviewed. Claims 36, 38-40, 42-45 and 50-52 are currently pending in the application. Claims 36, 38, 39, 45 and 52 were previously withdrawn from consideration. Claims 40, 42-44, 50, and 51 are under consideration. Claims 40, 42-44, 50, and 51 stand rejected. Reconsideration of the application is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 40, 42-44, 50, and 51 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Merten *et al.* (Production of influenza virus in cell cultures for vaccine preparation, *Exp. Med. Biol.* 1996, 397:141-51) (hereinafter "Merten") in view of Paul *et al.* (Increased viral titer through concentration of viral harvests from retroviral packaging lines, *Hum. Gene Ther.* 1993 Oct;4(5):609-15) (hereinafter "Paul"), in further view of Trudel *et al.* (Concentration and analysis of labile viruses by hollow fibre ultrafiltration and ultracentrifugation, *Process Biochem.*, Jan/Feb, 1983, pages 2-4 and 9) (hereinafter "Trudel"). Applicants respectfully traverse the rejections as hereinafter set forth.

The teachings of Merten and Paul are summarized in the Appeal Brief mailed July 18, 2006, and are incorporated herein. As to Trudel, the Examiner asserts that Trudel describes "that hollow fiber ultrafiltration is one of the most effective ways of achieving rapid viral concentration without loss of activity and that the method has been used on a number of viruses and that pore size is a consideration that effects flow rates." Office Action mailed November 2, 2006, at pages 3-4

No Motivation To Combine

With respect to each of the claims currently under consideration, there is no motivation to combine the references. The Examiner alleges that "one of ordinary skill in the art would have been motivated to clarify a supernatant and use a hollow fiber ultracentrifugation to concentrate the virus because gradient ultracentrifugation is a procedure that requires time, expensive materials, and expensive equipment." Office Action mailed July 27, 2005, pages 4-5. The

Examiner further asserts that “[o]ne of ordinary skill in the art would be motivated to purify large scale volumes of influenza as needed by Merton” and that “[o]ne of ordinary skill in the art would be motivated to use methods that are effective in concentrating large volumes of virus without loss of infectivity.” Office Action mailed November 2, 2006, at page 4. Applicants respectfully assert that the Examiner’s provided motivations are improper and believe that no motivation to combine the references exists.

Applicants respectfully submit that one would not be motivated to combine Paul with Merten or Trudel as there are still serious unexplained flaws in the hollow fiber ultracentrifugation of some viruses. As can be seen in Table 2 of Paul, certain unexplained changes caused by the isolation regime of Paul radically change the infectivity of the isolated retroviruses in regard to certain cell types. Specifically, the infection frequency on Jurkat cells is, at best, 37% of what is expected based on the titers determined on NIH-3T3 cells. In the worst example, the infection frequency is only 5% of what is expected. Such results strongly suggest that there is something in the isolation processing that is altering the virus in such a way that it has a much lower infection efficiency on cells it is known to infect. As such, one of skill in the art would not be motivated to use the isolation protocol of Paul as there are serious undefined effects of the process that can drastically alter viral function, with even more uncertain results when applied to influenza production.

While Trudel indicates success in isolating rubella virus and RSV, it does not remedy the process flaws evident in Paul. One ordinary skill in the art would understand that, while hollow fiber ultrafiltration works in the case of rubella virus and RSV, there are still serious unexplained flaws in the process which indicate that it is not equally applicable and useful for all virus types.

“[The] factual question of motivation is material to patentability and [cannot] be resolved on subjective belief and unknown authority.” *In re Lee*, 61, U.S.P.Q.2d, 1430, 1434 (Fed. Cir. 2002). “[T]he Board must not only assure that the requisite findings are made, based on evidence of record, but must also explain the reasoning by which the findings are deemed to support the agency’s conclusion.” *Id.* In the present case, the Examiner relies on an assertion that there is motivation to combine the references “because gradient ultracentrifugation is a procedure that requires time, expensive materials, and expensive equipment.” However, the

Examiner has provided no evidence of the time, expense, or equipment involved in gradient ultracentrifugation or in hollow fiber ultrafiltration. The Examiner seems to assert that the time, expense, and equipment involved for hollow fiber ultrafiltration would be decreased relative to that for ultra-centrifugation. However, the time required for hollow fiber centrifugation is substantial (2-6 hours) (Paul at page 610) and the hollow fiber methods require specialized filters and equipment including devices to regulate a constant pressure against the filter over the course of the purification (*Id.*). As such, applicants submit that the Examiner has not provided any reasoning or evidence to support his assertion that gradient ultracentrifugation is a more expensive procedure in terms of time, materials, and equipment. As such, in view of the ruling made in *In re Lee*, applicants submit that the Examiner has not provided a proper motivation to combine the references.

As to the Examiner's assertion that "[o]ne of ordinary skill in the art would be motivated to purify large scale volumes of influenza as needed by Merten," applicants respectfully assert that because one needs to purify large amounts of a virus does not provide motivation to select a specific purification scheme, let alone a scheme that has been shown to contain serious flaws with regard to certain virus types. The Examiner's assertions regarding motivation to combine the references indicate that it would be deemed obvious to purify any particular type of virus with any technique that has been shown applicable to the purification of any other kind of virus. Applicants respectfully assert that such motivations are improper as they point to no specific motivation in the art that one would choose a particular purification scheme to purify a particular type of virus. In addition, applicants respectfully submit that the Examiner relies on subjective belief and unknown authority if the Examiner intends to assert that because one needs to purify large amounts of influenza virus, one would be motivated to resort to hollow fiber ultrafiltration.

The Examiner further asserts that "[o]ne of ordinary skill in the art would be motivated to use methods that are effective in concentration large volumes of virus without loss of infectivity." Office Action mailed November 2, 2006, at page 4. However, as discussed *supra*, the art indicates hollow fiber ultrafiltration of virus may not lead to concentrating large volumes of virus without loss of infectivity. As shown by Paul, hollow fiber ultrafiltration resulted in

losses of infectivity ranging from 63% to 95%. Paul at Table 2. Consequently, applicants respectfully submit that the one of ordinary skill in the art would not be motivated to combine the references in order to concentrate influenza by hollow fiber ultrafiltration as hollow fiber ultrafiltration has been shown to result in substantial loss of infectivity for certain virus types.

The Examiner further asserts that the hollow fiber ultrafiltration methods taught in Paul are generally applicable. However, where Paul discusses the general applicability of the methods taught, the general applicability is related specifically to retrovirus preparation. *See, e.g.*, Paul at page 613, first sentence under “Discussion.” As such, the authors of Paul viewed their disclosure as generally relevant to retrovirus preparation, but make no teachings as to the relevance or applicability of the methods to the concentration of other virus types, such as influenza virus. Consequently, applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine Paul, Merten, and Trudel.

Trudel proposes the general applicability of hollow fiber ultrafiltration to labile enveloped viruses, however, Trudel only provides examples of rubella virus and RSV preparation. *See, e.g.*, Trudel at page 4, ¶¶ 1 and 2 under “Results and Discussion.” As such, though the authors of Trudel viewed their disclosure as generally relevant to labile enveloped virus preparation, their description is limited to rubella virus and RSV. However, Trudel makes no teachings as to the relevance or applicability of the methods to the concentration of other virus types or specifically influenza virus. Furthermore, the Examiner has provided no indication that an influenza virus would be considered a “labile enveloped virus” by one of ordinary skill in the art. Consequently, applicants respectfully submit that one of ordinary skill in the art would have not motivation to combine Paul or Merten with Trudel.

Furthermore, the broad assertion of Trudel that the methods are generally applicable to labile enveloped virus are made in absence of the knowledge of problems with hollow fiber ultrafiltration as noted by Paul. Trudel was published in the 1983 January/February issue of *Process Biochemistry* while Paul was not accepted for publication until June of 1993. As such, Trudel’s broad statements of applicability are made absent knowledge of the problems with hollow fiber ultrafiltration which are described by Paul. Consequently, applicants respectfully submit that Trudel’s broad statement regarding applicability does not reflect the state of the art at

the time the present application was filed. As such, applicants submit that Trudel's broad assertion that their methods are generally applicable to labile enveloped virus would not be motivation to combine the references at the time the present application was filed.

For at least the foregoing reasons, applicants respectfully submit that the Examiner has not provided the requisite proper motivation to combine the references, and that one of ordinary skill in the art would not be motivated to combine the references as they teach a process with serious flaws. As such, applicants respectfully request the withdrawal of the rejections of claims 40, 42-44, 50, and 51 under 35 U.S.C. § 103(a) and reconsideration of same.

No Reasonable Expectation of Success

The Examiner alleges that it would have been "obvious to concentrate the virus of Merten *et al.* using hollow fiber filtration with the expectation of success in increasing the concentration of influenza virus and purifying it." Office Action, mailed July 27, 2005, at page 5. The Examiner further asserts that "[o]ne of ordinary skill in the art at the time of the invention would have the expectation of success of using hollow fiber ultrafiltration knowing that it has been used to purify viruses and that it is thought to be one of the most rapid ways of concentrating virus without losing infectivity as taught by Trudel." Office Action, mailed November 2, 2004, at page 4. However, with respect to all of the claims under examination, applicants believe that no reasonable expectation of success exists in using the retroviral techniques of Paul, or the rubella virus and RSV techniques of Trudel, in the very different field of vaccine production for influenza virus. No indication is present in the cited references that the hollow fiber method as provided by Paul or Trudel would also be applicable to the disclosure of Merten or that the skilled person would be motivated by the teachings of the cited references to use hollow fiber filtration to purify an influenza virus.

Applicants submit that neither Paul or Trudel enables the concentration of influenza viruses using the described hollow fiber method, wherein such viruses remain infectious or can be made infectious. It would only be after burdensome experimentation and investigation that one of skill in the art could decide the utility of hollow fiber filtration for concentrating influenza virus. Moreover, Paul admits that the success of isolating infectious retroviral particles depends

on using specific filtration parameters and, even using those parameters, the retroviral infectivity was sometimes very low, presumably because of high shear forces (Paul at page 610). Further, the isolated retrovirus was inexplicably deficient at infecting certain cell types (*Id.* at Table 2). Accordingly, one of skill in the art would not have a reasonable expectation of success for concentrating influenza viruses that are infective or can be made infective under low shear conditions in view of the teachings of Paul with respect to retroviruses.

The Examiner further asserts that Trudel teaches that hollow fiber ultrafiltration is thought to be one of the most rapid ways of concentrating virus without losing infectivity. However, as noted *supra*, this assertion would not be given much weight by one of ordinary skill in the art as it was later shown by Paul that hollow fiber ultrafiltration may result in significant losses in infectivity. As such, applicants respectfully submit that one of ordinary skill in the art, at the time the application was filed, would not believe that a reasonable expectation of success existed based on the statements of Trudel as such a person would understand that those statements by Trudel had been superseded by the results of Paul.

In addition, applicants respectfully assert that, even though hollow fiber filtration was known at the time of the application, those of ordinary skill in the art knew that different filtration techniques were more or less appropriate depending on the type of virus to be isolated. The cited references make no indication that an influenza virus could be concentrated using a hollow fiber filter system or that one would obtain infectious influenza virus after using a hollow fiber filter. Retroviruses (as purified by Paul), rubella virus, and RSV (as purified by Trudel) may very well behave in a completely different manner than other viruses such as influenza virus. As there is no indication in the cited references that the hollow fiber method would work for influenza, applicants submit there would have been a need for an inventive step to provide a method as claimed in the present application.

In view of the forgoing, applicants respectfully submit that a *prima facie* case of obviousness has not been established as the cited references do not provide a reasonable expectation of success. Consequently, applicants respectfully request the withdrawal of the rejections of claims 40, 42-44, 50, and 51 under 35 U.S.C. § 103(a) and reconsideration of same.

References Do Not Teach Each And Every Element Of Claims 43 And 51

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all the claim elements. *In re Vaeck*, 0947 F.2d 488 (Fed. Cir. 1991). Applicants assert, that as to claims 43 and 51, the references fail to teach or suggest each and every element of the claims.

Claim 43 recites “the method according to claim 40, wherein said ultrafiltrating is performed with a filter comprising a cut-off of 750 KD.” Applicants assert that the references, when combined, do not teach or suggest the use of a filter having a cut-off of 750 KD for the use of concentrating an influenza virus. As asserted by the Examiner, Merten does not teach hollow fiber ultracentrifugation and Paul teaches the ultracentrifugation of retroviruses with a 500,000 MW cut-off (500 KD). Office Action mailed July 27, 2005, at page 4. The Examiner further asserts that the use of filters with cut-off values is known in the art of handling cell culture supernatants and the choice of a specific cut-off would be determined. *Id.* at page 5.

As admitted by the Examiner, the references do not teach or suggest the use of a filter having a cut-off of 750 KD. In an attempt to remedy this lack of teaching or suggestion, the Examiner appears to take official notice that one of ordinary skill in the art would choose a filter with a cut-off of 750KD for the concentration of influenza viruses based on the common knowledge of one of ordinary skill in the art. However, it is never appropriate to rely solely on “common knowledge” in the art without evidentiary support in the record. *In re Zurko*, 258 F.3d 1379, 1385 (CCPA 1979) (“[T]he Board cannot simply reach conclusions based on its own understanding or experiences, - or on its assessment of what would be basic knowledge or common sense. Rather the Board must point to some concrete evidence in the record in support of the findings”). “If the Examiner is relying on personal knowledge to support a finding of what is known in the art, the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding.” MPEP § 2144.04, citing 37 C.F.R. § 1.104(d)(2). If the Examiner is taking official notice of facts not in the record, then “the basis for such reasoning must be set forth explicitly” and the Examiner “must provide specific factual findings predicated on sound technical and scientific reasoning to support his or her conclusion of common knowledge.” MPEP 2144.03. Applicants submit that the Examiner has provided no

evidentiary support on the record that one of ordinary skill in the art would use a filter comprising a cut-off of 750 KD for the purification of influenza virus and that the Examiner has thus failed to show that "the choice of a specific cut-off would be determined" as being 750 KD.

In addition, applicants respectfully submit that Trudel does not make up for the lack of teaching a 750 KD filter and also teaches away from the use of such a filter. Trudel, at page 2, first paragraph, recommends the use of a 100 KD filter. As such, Trudel does not make up for the lack of teaching in Merten and Paul and specifically teaches that one should use a pore size of 100 KD.

In light of the foregoing remarks, applicants respectfully assert that the Merten, Paul, and Trudel, when combined, do not teach the use of a filter comprising a cut-off of 750 KD. Applicants further assert that the Examiners unsupported statement regarding the determination of a specific cut-off is without evidentiary support in the record and cannot properly form the basis of a rejection under 35 U.S.C. § 103(a). As such, applicants respectfully request that the rejection of claim 43 under 35 U.S.C. § 103(a) be withdrawn and the claim allowed.


Further as claim 51 depends from claim 43, applicants assert that claim 51 is at least allowable as depending from a non-obvious base claim. As such, applicants respectfully request that the rejection of claim 51 under 35 U.S.C. § 103(a) be withdrawn and the claim allowed.

CONCLUSION

In light of the above amendments and remarks, applicants respectfully request reconsideration of the application. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Attorney Docket No.: 2578-4626US

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Dan J. Morath', with a long horizontal flourish extending to the right.

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Date: February 2, 2007